
Exploration of neo-formed tissue using combining reactive poromechanics with computational cellular biology

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Abstract

1 - Objectives

Mechanobiology is focusing on how physical stimuli contribute to cell mechanotransduction, i.e the biochemical cell response due to a mechanical signal. Indeed, cell-cell and cell-matrix interactions might play a significant role into space and time evolution of extracellular matrix and beyond, to tissue and organ homeostasis or pathology. The same is true for understanding how biomaterials or cell seeded scaffolds work, whether they are designed for laboratory purposes or for in-vivo implantations. The interstitial flow can be considered as a stimulus for cells. However, advective properties of porous material are of particular interest when exploring in-situ response and interactions with host zone in biological environment. Cells population shows active migrations influenced by gradient growth-factors and capabilities to differentiate and produce extra-cellular matrix in presence of mechanical stimuli. Growth factors show diffusive properties in interstitial flow and matrix. These events are also conditioned by source terms such as vascularization bringing cells and nutrients among with growth factors. One of the key challenges is to predict extracellular matrix formation at the pore scale and beyond, as well as its evolution in space and time under biochemical and mechanical stimuli.

We hypothesized that the framework combining computational cell biology and reactive poromechanics to address this challenge. We have also provided a unique in vivo validation using a canine experimental model¹⁰ of implant healing. Among biophysical and clinical relevant output, the proposed methodology explained healing heterogeneity and stress-shielding frequently encountered and problematic in clinical arthroplasty.

2 - Materials and Methods

Poroelasticity define an effective medium formed of phases, namely the porous and deformable extra cellular matrix and the fluid fraction also representing the medium porosity. Continuity equations for darcean flow, i.e low filtration velocities, involved effective permeability associated with substrate porosity. Balance momentum due to loadings established combination of effective stress and fluid. Governing equations involved Lamé coefficients, namely elasticity properties and fluid pressure gradients.

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Cell populations were governed by advection-diffusion-reaction equations involving random motility, and active migrations, namely chemotactic migrations due to growth factors gradients influenced by fluid convection, and haptotactic migration due to evolution of local surface properties of extra-cellular matrix. Because of proliferation and extracellular matrix fabrication poromechanical response and cell populations responses were combined in space and time.

3 - Results

Governing equations were applied to the prediction of periprosthetic implant healing. Transport properties, namely diffusion coefficients, porosity and permeability as far as elastic properties of neo-formed tissue were explored as far as responses of osteoblastic phase and endothelial phase describing the neo-vascularization of the site. The role of transforming angiogenic factors and anabolic growth factors were considered. Theoretical and numerical results were compared to experimental studies in an animal model using segmented histological results.

4 - Conclusion

The combination of convective, diffusive and reactive effects nourished a wave front migration of extracellular matrix from the host bone to the implant but also from the implant to the host bone because of bioactive coating. The initial conditions were playing a major role and the model predicted a significant influence of cyclic implant motion on tissue formation. Concentrations of mineralized tissue at the implant at the implant surface and drill-hole similar to stress-shielding in the host bone were very well predicted by the model. Indeed, cell active migrations associated with mechanical strain are underlying crucial mechanisms playing reverse role in tissue formation.